

## **Non-technical abstract**

Progressive atherosclerosis in the peripheral arterial circulation leads to multi-segmental stenosis and occlusions causing peripheral arterial occlusive disease (PAOD). Consequently, arterial blood flow is reduced leading to ischemia in the affected extremities causing pain. Symptoms can progress further to include ulceration (skin breakdown) and gangrene (cell and tissue death) and at this stage treatment may require amputation. This study will evaluate the safety of increasing doses of an investigational angiogenic gene therapy product, Ad5.1FGF-4, in patients with PAOD Fontaine stage III (patients with leg pain at rest) and Fontaine stage IV (patients with leg ulcers or gangrene).

The study product Ad5.1FGF-4 is a growth factor gene (FGF-4) inserted in a carrier (modified adenovirus). The FGF-4 gene causes certain cells to produce a protein known as fibroblast growth factor 4 (FGF-4). In animal studies, FGF-4 has been found to stimulate the growth of new blood vessels (collaterals) in the leg. When Ad5.1FGF-4 is injected into the leg, the FGF-4 gene is carried into the muscle by the modified adenovirus. The modified adenovirus used in this study was derived from the adenovirus usually associated with the common cold. However, with gene transfer trials, the adenovirus part of the study product is been changed so it cannot grow and reproduce in normal human cells. Therefore, the usual symptoms of a natural adenoviral infection are unlikely to occur.

The study plan is to evaluate the safety and potentially beneficial effect of the Ad5.1FGF-4 treatment to increase the collateral blood vessels and blood flow in the leg and to find suitable doses for future studies. If effective, this treatment may improve blood flow in the legs, resulting in less claudication or rest pain, and possibly the decreased need for revascularization with surgery or angioplasty and even fewer or delayed amputations.

The study will be carried out in up to 15 different medical centers and will recruit up to 52 patients, 40 years-of-age or older. Study patients will still receive standard, necessary PAOD treatment during the study period. After successfully completing the screening procedures, study patients will be hospitalized and receive Ad5.1FGF-4 or placebo as 6 to 10 injections into the muscles of one symptomatic leg. Since the study is blinded, patients and their study doctors will not know whether they have received placebo or Ad5.1FGF-4. Each study patient will have a three in four (75%) chance of receiving Ad5.1FGF-4 and a one in four (25%) chance of receiving placebo. The overall study will use increasing doses of Ad5.1FGF-4 for patients in sequential groups, but each patient will receive only one dose. The lowest doses will be given to the first patient group and increased for subsequent groups, if no serious side effects are observed.

Each patient will take part in the study for three months after study product injection and will be required to return for 6 follow-up visits during that period. At these visits patients will complete lab tests, physical exams, leg assessments and various other procedures to evaluate the safety and effects of Ad5.1FGF-4. After the study visits have been completed, the study physician will forward patient information to the sponsor at 6, 12, 24 and 36 months after study product injection in order to assess the post-study outcome.